PATENT COOPERATION TREATY

REC'D 03 MAR 2005
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From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/US2004/038496	International filing date *(day/month/year)* 17.11.2004
Priority date *(day/month/year)* 17.11.2003	
International Patent Classification (IPC) or both national classification and IPC C12Q1/68	
Applicant PCT THERAPEUTICS, INC.	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/038496

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☐ The following document has not been furnished:

   ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☒ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 53-54 in part

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 53-54 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-44, 46-52
	No:	Claims	45, 53-54
Inventive step (IS)	Yes:	Claims	1-44, 47-52
	No:	Claims	45-46, 53-54
Industrial applicability (IA)	Yes:	Claims	1-54
	No:	Claims	None

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. **Claims 53-54** of the present application concern polypeptides characterised by their function without structural features. Therefore, it is unclear to the skilled person which polypeptide falls within the scope of the claim which is unlclear (**Article 6 PCT**). Considering page 38 of the description, it appears that some prefered polypetpides demonstrating the features of **claims 53-54** are listed. The search and examination has therefore been limited to these polypeptides.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. Reference is made to the following documents:
   D1: US-B1-6 465 176
   D2: JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 38, 1997, pages 23477-23480,
   D3: CANCER LETTERS, vol. 174, no. 2, 28 December 2001, pages 151-158,
   D4: WO 2004/065561 A

   D4 is an intermediate document published on August 2004, between the priority and filing date of the present application (**Rule 70.10 PCT**). Therefore **D4** is not considered to constitute prior art for the present application during the international phase. **D4** would become relevant with respect to novelty and inventive step during the national/regional phase to come if the priority of the present application is not valid.

3. **Novelty (Article 33(2) PCT):**
   3.1 **D1** (sequence 5, column 27; claim 1, 7) discloses a nucleic acid of 271 nucleotides having 98% homology with the SEQ ID 1 of the present application. This disclosure anticipates **claim 45** of the present application.
   3.2 **D2** (abstract) discloses a polypeptide corresponding to int-6 peptide which is disclosed in the application as filed as a preferred embodiment for the polypeptide

of the invention. **D2** is therefore considered to anticipate **claims 53-54** of the present application.

3.3 In order to summarise the above objections, **claims 45 and 53-54** are not novel and do not fulfil the requirements of **Article 33(2) PCT**, whereas **claims 1-44 and 46-52** are novel.

4. **Inventive merit (Article 33(3) PCT):**

4.1 **D3** (page 152, "Materials and methods"; page 156; abstract), which is the closest prior art, describes the inhibition of the overexpressed HER-2/neu gene by adding IRE in the 5'UTR of the gene. The method of the present **claim 1** distinguishes itself from **D3** in that the UTR used for modulating the gene expression corresponds to SEQ ID 1.

By using SEQ ID 1 as UTR to which the reporter gene is linked, the applicant established that this sequence is sufficient to reduce Her2 protein expression. Thus the problem to be solved is to determine a UTR of the Her2 gene which is sufficient for regulating the gene expression using a compound modulating the gene expression.

Since no document from the prior art discloses the SEQ ID 1 as a part of a UTR of Her2 gene, the skilled person would have no reason to suggest SEQ ID 1 as a solution to the given problem. In turn, the subject-matter of **claim 1** is considered to involve an inventive merit.

4.2 The same reasoning applies to independent **claims 21, 25 and 49** as well as to their dependent **claims 2-20, 22-24, 26-27 and 50-52** which are considered to involve an inventive merit.

4.3 As a consequence of the above, the cell line comprising a reporter gene linked to SEQ ID 1 (**claims 28-31**) or a hybrid comprising this sequence and another molecule (**claims 32-44**) as well as the nucleic acid consisting of SEQ ID 1 (**claims 47-48**) are also considered to involve an inventive merit.

4.4 **Claim 46** of the present application is considered not to involve an inventive merit over **D1** because this document teaches that such a sequence is known to be used in the modulation of gene expression.

4.5 In order to summarize the above, **claim 46** is not inventive and does not fulfil the requirements of **Article 33(3) PCT**, whereas **claims 1-44 and 47-52** are inventive.

5. **Industrial applicability (Article 33(4) PCT):**
An industrial applicability of the invention is obvious and **claims 1-54** of the present application are considered to fulfil the requirements of **Article 33(4) PCT**.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 2004/065561	05.08.2004	21.01.2004	21.01.2003

Re Item VII

Certain defects in the international application

6.1 Contrary to the requirements of **Rule 5.1(a)(ii) PCT**, the relevant background art disclosed in **D1-D3** are not mentioned in the description, nor are these documents identified therein.

6.2 Due to the high number of independent method claims, the present application is considered not to fulfil the requirements of **Rule 6.1(a) PCT**.

Re Item VIII

Certain observations on the international application

7. From the description, it appears that the methods of the present application can be performed in vivo. It is brought to the applicant's attention that such claims are not accepted in some contries.